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Letter to the Editor

Segmental Forms of Autosomal Dominant Skin Disorders: Different Types of Severity Reflect Different States of Zygosity

To the Editor:

Autosomal dominant skin disorders occasionally occur in a mosaic arrangement resulting from an early postzygotic mutation and involving the body in a quadrant, linear or otherwise segmental form [Hall, 1988; Happle, 1993]. The severity of lesions present in the circumscribed region mostly corresponds to that observed in the nonmosaic phenotype. Such cases have been reported, for example, in neurofibromatosis type 1 [Boltshauser et al., 1989], nevoid basal cell carcinoma syndrome [Shelley et al., 1969; Camisa et al., 1985] and epidermolytic hyperkeratosis of Brocq [Nazzaro et al., 1990; Paller et al., 1994].

However, sometimes the degree of involvement of the confined area is far more pronounced and, notably, the segmental lesions are superimposed on a milder, diffuse manifestation of the same phenotype. Such dichotomous forms of expression have been described in cases showing a linear arrangement of neurofibromatosis [Archer et al., 1988], cutaneous leiomyomatosis [Rudner et al., 1964; Mezzadra, 1965; Berendes et al., 1971], epidermolytic hyperkeratosis of Brocq [Hadlich and Linse, 1989], or porokeratosis, a disorder characterized by circular skin lesions showing central atrophy and a tiny keratotic ridge [Moreland and Wyre, 1981; Commens and Shumack, 1987; Happle, 1991]. To explain this phenomenon that has so far not attracted much attention, the following rule may be considered.

When an autosomal dominant skin disease occurs as a mosaic phenotype, two different types of manifestation, reflecting different states of zygosity, can be distinguished. Firstly, a mild type of involvement, corresponding to that encountered in the nonmosaic phenotype, reflects a heterozygous state of the underlying postzygotic mutation. Such cases may herald gonadal mosaicism, implying an increased risk such that in the following generation the same disorder may involve the entire body diffusely. Secondly, a severe type of manifestation would reflect loss of heterozygosity for the same allele. In this case an early postzygotic mutational event such as crossing over or nondisjunction occurring in a heterozygous embryo would give rise to a mosaic population of cells either homozygous or hemizygous for the allele.

Due to reduced penetrance, a heterozygous state for an autosomal dominant skin disorder may go unnoticed in a patient who may show, nevertheless, a severe type of mosaic manifestation resulting from allelic loss [Rimbaud et al., 1964; Happle, 1991; Camacho et al., 1994].

A similar mechanism was proposed previously to explain a severe mosaic manifestation of genetic diseases involving internal organs [Gardner et al., 1988; Hall et al., 1988]. Future molecular research should show whether this dichotomy according to the state of zygosity holds true.

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